

**Amendments to the Specification:**

Please replace the paragraph spanning lines 32 to 34 of page 68 and lines 1 to 3 of page 69 with the following new paragraph:

For example, a duplex comprising an antisense oligomeric compound having the sequence CGAGAGGCGGACGGGACCG (SEQ ID NO:36) and having a two-nucleobase overhang of deoxythymidine(dT) would have the following structure:

**cgagagggcgacggacgdTdT Antisense (SEQ ID NO:37)**  
||||||| Strand  
**dTdTGctctccgctgcctggc Complement Strand (SEQ ID NO:38)**

Please replace the paragraph spanning lines 26 to 33 of page 81 and lines 1-10 of page 82 with the following new paragraph:

The activity of selected double stranded compositions was determined against % PTEN mRNA levels (normalized to RiboGreen, Hela Cells, dose response at 0.6 nM, 3.0 nM, 15 nM and 75 nM). Eight duplex siRNA's were compared to the untreated control. The antisense strands were full PO blunt or with dTdT overhangs and full PS blunt. The sense strands used were full P=O RNA or full 2'-O-CH<sub>3</sub> 20 mers either full P=O or full P=S.

| <u>SEQ ID NO:/ISIS NO's:</u> | <u>Description antisense/sense</u> | <u>Dose</u> | <u>PTEN mRNA Level</u> |
|------------------------------|------------------------------------|-------------|------------------------|
| N/A                          | Untreated control                  | 0.00        | 1.00                   |
| <u>1/335449/2/308746</u>     | P=O RNA/P=O RNA                    | 75          | 0.25 (blunt ends)      |
| <u>1/303912/2/308746</u>     | P=S RNA/P=O RNA                    | 75          | 0.25 (blunt ends)      |
| <u>1/335449/2/330696</u>     | P=O RNA/P=O 2'-O-CH <sub>3</sub>   | 75          | 0.40 (blunt ends)      |
| <u>1/303912/2/330696</u>     | P=S RNA/P=O 2'-O-CH <sub>3</sub>   | 75          | 0.23 (blunt ends)      |
| <u>1/335449/2/341315</u>     | P=O RNA/P=S 2'-O-CH <sub>3</sub>   | 75          | 0.33 (blunt ends)      |
| <u>1/303912/2/341315</u>     | P=S RNA/P=S 2'-O-CH <sub>3</sub>   | 75          | 0.21 (blunt ends)      |
| <u>8/297803/9/271784</u>     | P=O RNA/P=O RNA                    | 75          | 0.14 (3'-dTdT ends)    |
| <u>8/297803/9/334465</u>     | P=O RNA/P=O 2'-O-CH <sub>3</sub>   | 75          | 0.46 (3'-dTdT ends)    |

Please replace the paragraph spanning lines 25 to 29 of page 83 with the following new paragraph:

The rank order of the 3 constructs is shown below:

| <b><u>Order</u></b> | <b><u>SEQ ID NO:/ISIS NO's as/s</u></b> | <b><u>as/s strands</u></b>       |
|---------------------|---|----------------------------------|
| 1                   | <u>1/331693/2/308746</u>                | 5'-P P=O/P=O                     |
| 2                   | <u>2/326908/2/330696</u>                | 5'-P P=S/P=O 2'-OCH <sub>3</sub> |
| 3                   | <u>2/326908/2/308746</u>                | 5'-P P=S/P=O                     |

Please replace the paragraph spanning lines 3 to 16 of page 84 with the following new paragraph:

The activities of selected siRNA compositions were determined relative to reduction of PTEN mRNA levels (Hela Cells, 175 nM doses). Each of the siRNA compositions had an RNA antisense strand having either P=O or P=S internucleoside linkages with the sense strand set as full P=O 2'-O-CH<sub>3</sub> with or without a 3'-biotin group.

| <b><u>SEQ ID NO:/ISIS NO's:</u></b> | <b><u>Description antisense/sense</u></b> | <b><u>PTEN mRNA Level</u></b> |
|-------------------------------------|---|-------------------------------|
| N/A                                 | Untreated control                         | 1.00                          |
| <b><u>29592 SITE</u></b>            |   |                               |
| <u>1/303912/2/330696</u>            | P=S RNA/P=O 2'-O-CH <sub>3</sub>          | 0.19                          |
| <u>1/326908/2/330696</u>            | P=S RNA/P=O 2'-O-CH <sub>3</sub> 3'-Bi    | 0.17                          |
| <u>1/331693/2/330696</u>            | P=O RNA/P=O 2'-O-CH <sub>3</sub> 3'-Bi    | 0.28                          |
| <b><u>116847 SITE</u></b>           |   |                               |
| <u>5/300857/7/290224</u>            | P=S RNA/P=O 2'-O-CH <sub>3</sub>          | 0.19                          |
| <u>6/271766/7/290224</u>            | P=O RNA/P=O 2'-O-CH <sub>3</sub>          | 0.54                          |

Please replace the paragraph spanning lines 11 to 24 of page 85 with the following new paragraph:

The activities of selected siRNA's compositions were determined relative to reduction of PTEN mRNA levels (Hela Cells, 5, 20 and 50 nM doses). Three compositions, two targeted to the 116847 site and one targeted to the 29592 site were examined with the sense strand in each case being a full P=O 2'-O-CH<sub>3</sub>. The unmodified RNA/RNA control was targeted to the 116847 site.

| <u>SEQ ID NO:/ISIS NO's:</u> | <u>Description antisense/sense</u> | <u>PTEN mRNA Level</u> |
|------------------------------|------------------------------------|------------------------|
| N/A                          | Untreated control                  | 1.00                   |
|                              |                                    | <u>116847 SITE</u>     |
| <u>6/271766/7/271790</u>     | P=O RNA/P=O RNA                    | 0.17                   |
| <u>6/271766/7/290224</u>     | P=O RNA/P=O 2'-O-CH <sub>3</sub>   | 0.80                   |
| <u>5/300857/7/290224</u>     | P=S RNA/P=O 2'-O-CH <sub>3</sub>   | 0.27                   |
|                              |                                    | <u>29592 SITE</u>      |
| <u>1/303912/2/330696</u>     | P=O RNA/P=O 2'-O-CH <sub>3</sub>   | 0.16                   |

Please replace paragraph spanning lines 18 to 30 of page 86 with the following new paragraph:

The activity of various compositions targeted to the 29592 site of PTEN was determined as normalized to cRAF (2, 10, and 50 nM doses).

| <u>SEQ ID NO:/ISIS NO's:</u> | <u>Description antisense/sense</u>             | <u>PTEN mRNA Level</u> |
|------------------------------|--|------------------------|
| N/A                          | Untreated control                              | 1.00                   |
| <u>8/297803/9/271784</u>     | P=O RNA/P=O RNA (3'-dTdT's)                    | 0.15                   |
| <u>8/297803/9/334465</u>     | P=O RNA/P=O 2'-O-CH <sub>3</sub> (3'-dTdT's)   | 0.53                   |
| <u>1/335449/2/308746</u>     | P=O RNA/P=O RNA (blunt ended)                  | 0.22                   |
| <u>1/335449/2/330696</u>     | P=O RNA/P=O 2'-O-CH <sub>3</sub> (blunt ended) | 0.30                   |

|   |  |      |
|---|--|------|
| <u>1/303912/2/308746</u>                      | P=S RNA/P=O RNA (blunt ended)                  | 0.25 |
| <u>1/303912/2/330696</u><br><del>303696</del> | P=S RNA/P=O 2'-O-CH <sub>3</sub> (blunt ended) | 0.28 |

Please replace the paragraph spanning lines 17 to 32 of page 87 and lines 1 to 5 of page 88 with the following new paragraph:

The activities of selected siRNA compositions were determined relative to reduction of PTEN mRNA levels (normalized to Ribogreen, Hela Cells, .6, 3, 15 and 75 nM doses, activity in table from 75 nM dose). All of the compositions were targeted to the 116847 site. The activities of the compositions were compared to untreated control, unmodified RNA having 3'-dTdT overhangs and the same RNA having P=S linkages in the antisense strand. The five compositions examined all had full 2'-O-methyl P=O sense strands. The antisense strands were P=O and P=S blunt, P=O and P=S with dTdT overhangs and one antisense strand was P=S blunt with a 3'-biotin group.

| <u>SEQ ID NO:/ISIS NO's:</u>     | <u>Description antisense/sense</u>  | <u>PTEN mRNA Level</u>  |
|----------------------------------|-------------------------------------|-------------------------|
| N/A                              | Untreated control                   | 1.00                    |
|                                  |                                     | <u>116847 SITE</u>      |
| <u>6/271766/7/271790</u>         | P=O RNA/P=O RNA                     | 0.30 (dTdT ended)       |
| <u>6/344185/7/271790</u>         | P=S RNA/P=O RNA                     | 0.36 (dTdT ended)       |
| <u>6/271766/7/290224</u>         | P=O RNA/P=O 2'-O-CH <sub>3</sub>    | 0.90 (dTdT ended)       |
| <u>6/271766/300857/15/344184</u> | P=O RNA/P=O 2'-O-CH <sub>3</sub>    | 0.45 (blunt ended)      |
| <u>6/344185/7/290224</u>         | P=S RNA/P=O 2'-O-CH <sub>3</sub>    | 0.39 (dTdT ended)       |
| <u>5/300857/15/344184</u>        | P=S RNA/P=O 2'-O-CH <sub>3</sub>    | 0.53 (Blunt ended)      |
| <u>5/300857/7/290224</u>         | P=S RNA Bi/P=O 2'-O-CH <sub>3</sub> | 0.40 (Blunt/dTdT ended) |

Please replace paragraph spanning lines 30 to 33 of page 88 and lines 1 to 8 of page 89 with the following new paragraph:

The activity of the RNA P=O/P=O versus the P=O/P=O-2'-O-Methyl constructs was examined (% mRNA PTEN, normalized to cRAF, 2, 10 and 50 nM doses) at three separate sites (29592, 29593 and 29597). All sequences are 3'-dTdT.

| <u>SEQ ID NO's/ISIS NO's:</u>   | <u>Description antisense/sense</u> | <u>PTEN mRNA Level</u> |
|---------------------------------|------------------------------------|------------------------|
| N/A                             | Untreated control                  | 1.00 (29592 site)      |
| <u>8/297803/9/271784</u>        | P=O RNA/P=O RNA                    | 0.32                   |
| <u>8/297803/344179/9/334465</u> | P=S RNA/P=O RNA                    | 0.78                   |
| <u>19/297804/17/271785</u>      | P=O RNA/P=O 2'-O-CH <sub>3</sub>   | 0.29                   |
| <u>19/297804/17/334466</u>      | P=O RNA/P=O 2'-O-CH <sub>3</sub>   | 0.68                   |
| <u>16/297807/18/271788</u>      | P=S RNA/P=O 2'-O-CH <sub>3</sub>   | 0.17                   |
| <u>16/297807/18/334470</u>      | P=S RNA/P=O 2'-O-CH <sub>3</sub>   | 0.18                   |

Please replace the paragraph spanning lines 33 to 34 of page 89 and lines 1-16 of page 90 with the following new paragraph:

The activity of the RNA P=O(S)/P=O versus the P=O(S)/P=O-2'-O-Methyl constructs was examined (% mRNA PTEN, normalized to Ribogreen, .6, 3, 15, and 75 nM doses). The unmodified sequences were full P=O with 3'-dTdT overhangs. The full P=O 2'-O-methyl constructs were prepared with 3'-dTdT overhangs and with blunt ends. The full P=S antisense having full P=O 2'-O-methyl constructs were prepared with 3'-dTdT overhangs and with 3'-dTdT overhangs in the antisense strand with a blunt end in the sense strand. Activities are shown at the 75 nM dose.

| <u>SEQ ID NO's/ISIS NO's:</u> | <u>Description antisense/sense</u> | <u>PTEN mRNA Level</u> |
|-------------------------------|------------------------------------|------------------------|
| N/A                           | Untreated control                  | 1.00 (29593 site)      |
| <u>19/297804/17/271785</u>    | P=O RNA/P=O RNA                    | 0.14 (3'-dTdT)         |

|                            |                                  |      |                 |
|----------------------------|----------------------------------|------|-----------------|
| <u>19/297804/17/334466</u> | P=O RNA/P=O 2'-O-CH <sub>3</sub> | 0.69 | (3'-dTdT)       |
| <u>19/344180/17/271785</u> | P=S RNA/P=O RNA                  | 0.87 | (3'-dTdT)       |
| <u>19/344180/17/334466</u> | P=S RNA/P=O 2'-O-CH <sub>3</sub> | 0.72 | (3'-dTdT)       |
| <u>20/334468/21/334467</u> | P=O RNA/P=O 2'-O-CH <sub>3</sub> | 0.25 | (blunt)         |
| <u>19/344180/21/334467</u> | P=S RNA/P=O 2'-O-CH <sub>3</sub> | 1.03 | (3'-dTdT/blunt) |
| <u>22/116846</u>           | 5/10/5 MOE gapmer                | 0.32 |                 |

Please replace the paragraph spanning lines 4 to 16 of page 91 with the following new paragraph:

The activities of constructs having all the different combinations of P=O(S)/P=O(S) (2'-O-Methyl) were determined (% mRNA PTEN, normalized to Ribogreen, .6, 3, 15, and 75 nM doses). Activities are shown at the 75 nM dose. All sequences are 3'-dTdT.

| <u>SEQ ID NO:/ISIS NO's:</u> | <u>Description antisense/sense</u> | <u>PTEN mRNA Level</u> |
|------------------------------|------------------------------------|------------------------|
| N/A                          | Untreated control                  | 1.00 (29597 site)      |
| <u>16/297807/18/271788</u>   | P=O/P=O RNA                        | 0.25                   |
| <u>16/344182/18/344181</u>   | P=S/P=S RNA                        | 0.33                   |
| <u>16/297807/18/334470</u>   | P=O RNA/P=O 2'-O-CH <sub>3</sub>   | 0.22                   |
| <u>16/297807/18/344183</u>   | P=O RNA/P=S 2'-O-CH <sub>3</sub>   | 0.79                   |
| <u>16/344182/18/334470</u>   | P=S RNA/P=O 2'-O-CH <sub>3</sub>   | 0.81                   |
| <u>16/344182/18/344183</u>   | P=S RNA/P=S 2'-O-CH <sub>3</sub>   | 0.69                   |

Please replace the paragraph spanning lines 24 to 30 of page 99 with the following new paragraph:

For example, a duplex comprising an antisense strand having the sequence CGAGAGGCGGACGGGACCG (SEQ ID NO:36) and having a two-nucleobase overhang of deoxythymidine(dT) would have the following structure:

**cgagagcgggacggacgdTdT Antisense Strand (SEQ ID NO:37)**

|||||

**dTdTgtctcgcctgcctggc Complement Strand (SEQ ID NO:38)**

Please replace the Table beginning at line 20 of page 119 and lines 1-2 of page 120 with the following new Table:

Table 4

| Construct design<br>(antisense:sense) | SEQ ID NO:/Isis<br>Numbers<br>(antisense + sense) | Sample | Dose of construct |      |       |       |
|---------------------------------------|---|--------|-------------------|------|-------|-------|
|                                       |   |        | 0.6 nM            | 3 nM | 15 nM | 75 nM |
| PO:PO                                 | <u>1/335449</u> + <u>2/308746</u>                 | A      | 94                | 69   | 32    | 21    |
| PO:PS                                 | <u>1/335449</u> + <u>2/344178</u>                 | B      | 103               | 60   | 25    | 23    |
| PO:PO_2'Omc                           | <u>1/335449</u> + <u>2/330696</u>                 | C      | 129               | 92   | 54    | 44    |
| PO:PS_2'Omc                           | <u>1/335449</u> + <u>2/341315</u>                 | D      | 109               | 67   | 27    | 31    |
| PO:PO_MOE                             | <u>1/335449</u> + <u>2/356426</u>                 | E      | 143               | 123  | 72    | 76    |
| PO:PS_MOE                             | <u>1/335449</u> + <u>2/356427</u>                 | F      | 119               | 79   | 40    | 44    |
| Mismatch                              | <u>23/308745</u> + <u>24/354622</u>               |        | 128               | 134  | 95    | 83    |
| PS:PO                                 | <u>1/303912</u> + <u>2/308746</u>                 | G      | 120               | 80   | 28    | 25    |
| PS:PS                                 | <u>1/303912</u> + <u>2/344178</u>                 | H      | 110               | 66   | 23    | 25    |
| PS:PO_2'Omc                           | <u>1/303912</u> + <u>2/330696</u>                 | I      | 119               | 78   | 24    | 29    |
| PS:PS_2'Omc                           | <u>1/303912</u> + <u>2/341315</u>                 | J      | 78                | 62   | 31    | 27    |
| PS:PO_MOE                             | <u>1/303912</u> + <u>2/356426</u>                 | K      | 83                | 60   | 45    | 24    |
| PS:PS_MOE                             | <u>1/303912</u> + <u>2/356427</u>                 | L      | 97                | 106  | 99    | 106   |

Please insert the sequence listing being filed concurrently herewith into the specification.